REMARKS

Applicants respectfully request entry of the present amendments to the claims and consideration of the following remarks.

STATUS OF CLAIMS

Claims 1-3 and 6-15 are pending. Claims 1, 3, 8, and 15 are amended. Claim 19 is new. Claim 1 has been amended to include the term "about" before the numerical values relating to pH. Support for this amendment may be found throughout the specification, for example, at page 9, lines 15-17. Claim 1 has also been amended to include the "polyol" limitation of claim 3. Further, claim 1 has been amended to replace the term "aqueous" with "liquid." This amendment is supported throughout the specification, for example, at page 3, lines 27-28. Claim 8 is amended to correct claim dependency. Claim 15 is amended to correct a typographical error. New claim 19 find support throughout the specification, for example, at page 9, lines 15-17 and original claim 1. No new matter has been added.

REJECTION UNDER § 102(B)

Claims 1, 3, 6, 7, 12, and 13 are rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by US 6,432,449 (Goldenberg). This rejection is respectfully traversed.

The present disclosure relates to stable pharmaceutical compositions of a protein, granulocyte-colony stimulating factor (G-CSF). The G-CSF of the present disclosure is expressed heterologously in the bacteria *E. coli*, and thus is produced in a non-glycosylated form. G-CSF, and especially non-glycosylated G-CSF, is known to be a hydrophobic protein, typically insoluble under biological conditions. Non-glycosylated G-CSF is known to be relatively unstable in *in vitro* preparations, having a tendency to form non-bioactive aggregations, so various additives have been proposed with respect to prior preparations in order to increase the stability and solubility of the protein, and aid in preventing aggregate formation. These additives may be undesirable for use in

pharmaceutical preparations, however, as described in page 3, fifth full paragraph of the specification. The present invention therefore provides a method of producing liquid pharmaceutical preparations of biologically active, recombinant, non-glycosylated G-CSF having a relatively long shelf life, without the use of any surfactants.

Independent claim 1 defines a stable pharmaceutical composition of G-CSF, wherein the composition has a pH value in the range from about 4.2 to about 4.8 and comprises a therapeutically effective amount of non-glycosylated G-CSF, a polyol, and an acid, wherein the composition is free of a surfactant, and wherein the composition is liquid. Applicants have found that the claimed pharmaceutical composition is stable in liquid form, has a long shelf life, is physiologically well-tolerated, is simple to use, and is amenable to be dosed precisely. (See page 3, lines 27-32).

Goldenberg

Goldenberg discloses a sustained release formulation using biodegradable alginate delayed gels or particles and methods thereof. Example 5 was referenced in the Office Action as allegedly anticipatory. However, the gel formulated in Example 5 does not anticipate the scope of present claim 1 for at least the reasons that it does not contain a polyol and it is not a liquid pharmaceutical composition.

The previous Office Action stated "the ethyl ester alginate is only one third esterified and according to the definition of the polyol in the instant specification, is a polyol." The present specification defines a polyol as "any polyhydric alcohol." Partially esterified ethyl ester alginate is not a polyhydric alcohol as called for in the claims, but is a carboxylic acid polymer. One of ordinary skill in the art would not regard the alginate as a polyol or a polyhydric alcohol, since it is not an alcohol containing one or more hydroxyl groups. Therefore, Example 5 of Goldenberg does not disclose a polyol as required by claim 1.

The present claim 1 also calls for a liquid pharmaceutical composition. Nothing in Goldenberg discloses or teaches such a composition. Goldenberg teaches the formation of gels. While the materials in Goldenberg might be liquid at some point

during their manufacture, they are not disclosed or taught to be stable in liquid form. The liquid state is only temporary, being described in Goldenberg as "liquid mixtures for time delay gelation." (See for example, column 3, lines 51-56; column 4, lines 13-15; column 10, lines 43-50; column 10, lines 55-61; and Example 5). The pre-gelled state of the Goldenberg compositions is a transitory, unstable intermediate stage in the process, and not a stable pharmaceutical composition as claimed.

Therefore, claim 1 and dependent claims 3, 6-7, 12, and 13 are plainly not anticipated by Goldenberg. Further, new claim 19, being dependent from claim 1, is likewise novel over Goldenberg. Reconsideration and allowance of claims 1, 3, 6-7, 12, and 13 are hereby respectfully requested.

REJECTIONS UNDER § 103(A)

Claims 1-3, 6-9, and 12-15 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over US 6,875,432 (Liu) in view of US 5,284,656 (Platz) and in further view of US 6,776,983 (Sumida). This rejection is respectfully traversed.

Independent claim 1 defines a stable pharmaceutical liquid composition of granulocyte-colony stimulating factor (G-CSF), wherein the composition has a pH value in the range from about 4.2 to about 4.8 and comprises a therapeutically effective amount of non-glycosylated G-CSF, a polyol, and an acid, wherein the composition is free of a surfactant, and wherein the composition is liquid. The claimed liquid pharmaceutical composition is shown to exhibit a long shelf life, to be physiologically well-tolerated, to be simple to use, and to be dosible more precisely. (See page 3, lines 27-32).

Surfactants have been disclosed for inclusion in G-CSF formulations to prevent aggregation and denaturation at packing material surfaces. One of skill in the art reading Liu, Platz, and Sumida would be taught to include a surfactant in their respective compositions according to what is conventional in the art. One would not be

led from any of these references (or any combination of them) to exclude surfactants from a composition otherwise meeting the requirements of the pending claims.

Liu discloses a concentrated protein formulation with reduced viscosity suitable for subcutaneous administration. (See Abstract). Liu discloses that it is preferable to include a surfactant in its protein formulations (see column 25, lines 18-40). Further surfactants are included in at least Examples 1-4. Therefore, one of skill in the art reading Liu would be led to use a surfactant in a final formulation.

Platz discloses compositions of G-CSF suitable for pulmonary administration, i.e., aerosol administration. Platz teaches away from delivery of G-CSF by injection, and instead disclose "an effective non-invasive" pulmonary administration of G-CSF. (See column 2, lines 60-62). Surfactants are repeatedly taught throughout Platz, for example, see column 3, line 62 through column 4, line 3; column 4, lines 6-17; and column 7, lines 16-22. Further, surfactants were included in all representative examples. (See Table 2 and column 8, line 66 through column 9, line 31). (Note that this is in spite of the fact that surfactants were found to not be necessary in aerosol formulations, see Column 8, lines 1-14).

While one of skill in the art reading Liu would not necessarily have any reason to seek the guidance of Platz as the two references are directed to two entirely different drug delivery formulations, one who happened to read both formulations would still be taught to include a surfactant. Purely for the sake of argument, if one were to combine Liu with Platz, one of skill in the art would still be motivated to include a surfactant in the final formulation.

Sumida discloses a stable G-CSF formulation comprising a G-CSF and at least one pharmaceutically acceptable surfactant. The formulation is also taught to have a pH in the range of 6-6.8 (see claim 1). Further, the formulation is disclosed as being substantially free from protein as a stabilizer.

Firstly, one of ordinary skill in the art reading Liu would be very unlikely to seek the guidance of Sumida without first having knowledge of the Applicants' application, since G-CSF is one listed protein in a laundry list of at least 100 named suitable proteins. Further, Sumida discloses a formulation that is free of proteins used as stabilizers. Liu, on the other hand discloses Zn-protein complexes as suitable stabilizers. (See column 25, lines 52-58). The only way to consider combining the two references is upon impermissible hindsight after reading the Applicants application.

For the sake of argument, even if one were to combine Liu with Sumida, one would not arrive at the presently claim 1. Liu and Platz disclose the use of a surfactant as a preferred component. Sumida requires the use of a surfactant in its formulations. Therefore, one reading Liu, Platz, and Sumida together would be taught to include a surfactant in a resulting formulation. This is outside the scope of present claim 1, which requires the composition to be free of a surfactant.

Therefore, independent claim 1 and its dependent claims 2-3 and 6-15 are nonobvious in view of Liu in view of Platz and in further view of Sumida. Reconsideration and allowance of claims 1-3 and 6-15 are hereby respectfully requested. For similar reasons, new claim 19 is likewise nonobvious over the cited references.

Nonstatutory Obviousness-type Double Patenting Rejection

Claims 1-3 and 8-11 are "provisionally" rejected over claims 1-10 of copending Application No. 10583157. Copending Application No. 10583157 claims a priority date of December 23, 2003. The present application claims a priority date of November 4, 2003. Since copending Application No. 10583157 has not yet undergone substantive examination and it is the later-filed application, Applicants submit that should the conditions still warrant, a nonstatutory obviousness-type double patenting rejection (and the possible need for a Terminal Disclaimer) would be proper in copending Application No. 10583157 rather than the present application.

Should the Applicants be incorrect in their assumptions and should the nonstatutory obviousness double patenting rejection be the only remaining rejection, the Applicants would then submit a proper terminal disclaimer in accordance with 37 CFR 1.321(c) to remove the rejection, upon allowance of claims in a prior-filed co-pending application. Accordingly, reconsideration and allowance of claims 1-3 and 8-11 are hereby respectfully requested.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

FEES

The Applicants do not believe that there are any fees associated with this filing. However, if the calculations are incorrect, the Commissioner is hereby authorized to charge any deficiencies in fees or credit any overpayment associated with this communication to Deposit Account No. 12-2355. Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 12-2355.

Respectfully submitted,

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